

CLAIMS

We Claim:

1. An antimicrobial sulfonamide derivative, or a salt or a hydrate thereof,
5 comprising:
a core cyclic peptide or core antibiotic of a lipopeptide antibiotic; and
a lipophilic moiety,
wherein said lipophilic moiety is covalently attached to the core cyclic peptide or core
cyclic antibiotic via a linking chain which includes a sulfonamide linkage.

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2. The antimicrobial sulfonamide derivative, salt or hydrate of Claim 1 in which
the linking chain is a sulfonamide linkage.

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3. The antimicrobial sulfonamide derivative, salt or hydrate of Claim 1 in which
the linking chain is a linker that links the core cyclic peptide or core antibiotic to the lipophilic
moiety.

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4. The antimicrobial sulfonamide derivative, salt or hydrate of Claim 1 which is a
compound according to structural Formula (I):



wherein:

Y is a lipophilic moiety;

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Each X is independently selected from the group consisting of —CO—
—SO₂—, —CS—, —PO—, —OP(O)—, —OC(O)—, —NHCO— and —N(R¹)CO— with the
proviso that at least one X is —SO₂—;

m is 0 or 1;

L is a linker;

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N is nitrogen;

R¹ and R⁴ are each independently selected from the group consisting of
hydrogen, (C₁-C₂₅) alkyl optionally substituted with one or more of the same or different R²

groups, (C_1 - C_{25}) heteroalkyl optionally substituted with one or more of the same or different R^2 groups, (C_5 - C_{30}) aryl optionally substituted with one or more of the same or different R^2 groups, (C_5 - C_{30}) arylaryl optionally substituted with one or more of the same or different R^2 groups, (C_5 - C_{30}) biaryl optionally substituted with one or more of the same or different R^2 groups, five to thirty membered heteroaryl optionally substituted with one or more of the same or different R^2 groups, (C_6 - C_{30}) arylalkyl optionally substituted with one or more of the same or different R^2 groups and six to thirty membered heteroarylalkyl optionally substituted with one or more of the same or different R^2 groups;

each R^2 is independently selected from the group consisting of —OR³,
—SR³, —NR³R³, —CN, —NO₂, —N₃, —C(O)OR³, —C(O)NR³R³, —C(S)NR³R³,
—C(NR³)NR³R³, —CHO, —R³CO, —SO₂R³, —SOR³, —PO(OR³)₂, —PO(OR³), —CO₂H,
—SO₃H, —PO₃H, halogen and trihalomethyl;

each R^3 is independently selected from the group consisting of hydrogen, (C_1 - C_6) alkyl, (C_5 - C_{10}) aryl, five to sixteen membered heteroaryl, (C_6 - C_{16}) arylalkyl
and six to sixteen membered heteroarylalkyl; and

R is a core cyclic peptide or core antibiotic of a lipopeptide antibiotic.

5. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core cyclic peptide of laspartomycin, zaomycin, crystallomycin, aspartocin, amphotomycin,
20 glumamycin, brevistin, cerexin A, cerexin B, Antibiotic A-30912, Antibiotic A-1437,
Antibiotic A-54145, Antibiotic A-21978C or tsushimycin.

6. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core antibiotic of laspartomycin, zaomycin, crystallomycin, aspartocin, amphotomycin, glumamycin,
25 brevistin, cerexin A, cerexin B, Antibiotic A-30912, Antibiotic A-1437, Antibiotic A-54145,
Antibiotic A-21978C or tsushimycin.

7. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core cyclic peptide of laspartomycin, aspartocin, Antibiotic A-30912, Antibiotic A-1437, Antibiotic
30 A-54145 or Antibiotic A-21978C.

8. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core

antibiotic of laspartomycin, aspartocin, Antibiotic A-30912, Antibiotic A-1437, Antibiotic A-54145 or Antibiotic A-21978C.

9. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core
5 cyclic peptide of laspartomycin or aspartocin.

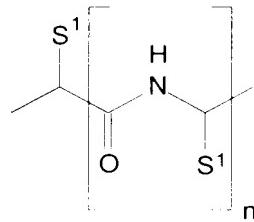
10. The antimicrobial sulfonamide derivative of Claim 4 in which R is the core
antibiotic of laspartomycin or aspartocin.

11. The antimicrobial sulfonamide derivative of Claim 4 in which m is 1.

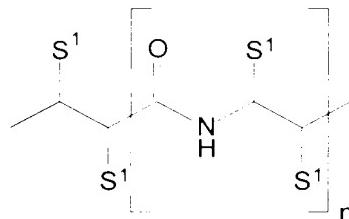
12. The antimicrobial sulfonamide derivative of Claim 4 in which R¹ and R⁴ are
hydrogen.

15 13. The antimicrobial sulfonamide derivative of Claim 4 in which L is selected
from the group consisting of:

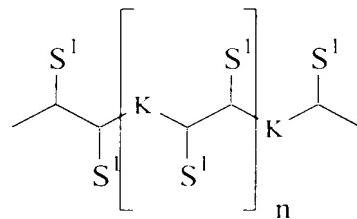
20 (L1)



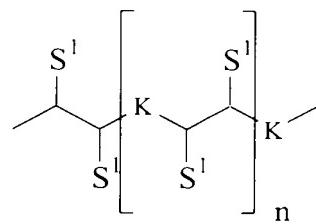
(L2)



25 (L3)



5 (L4)



or a pharmaceutically acceptable salt or hydrate thereof, wherein:

n is 0, 1, 2 or 3;

each S¹ is independently selected from the group consisting of hydrogen, (C₁-C₁₀) alkyl optionally substituted with one or more of the same or different R⁵ groups, (C₁-C₁₀) heteroalkyl optionally substituted with one or more of the same or different R⁵ groups, (C₅-C₁₀) aryl optionally substituted with one or more of the same or different R⁵ groups, (C₅-C₁₅) arylaryl optionally substituted with one or more of the same or different R⁵ groups, (C₅-C₁₅) biaryl optionally substituted with one or more of the same or different R⁵ groups, five to ten membered heteroaryl optionally substituted with one or more of the same or different R⁵ groups, (C₆-C₁₆) arylalkyl optionally substituted with one or more of the same or different R⁵ groups and six to sixteen membered heteroarylalkyl optionally substituted with one or more of the same or different R⁵ groups;

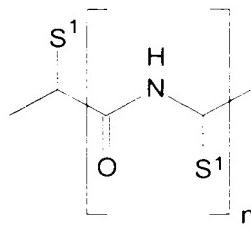
each R⁵ is independently selected from the group consisting of —OR⁶, —SR⁶, —NR⁶R⁶, —CN, —NO₂, —N₃, —C(O)OR⁶, —C(O)NR⁶R⁶, —C(S)NR⁶R⁶, —C(NR⁶)NR⁶R⁶, —CHO, —R⁶CO, —SO₂R⁶, —SOR⁶, —PO(OR⁶)₂, —PO(OR⁶), —CO₂H, —SO₃H, —PO₃H, halogen and trihalomethyl;

each R⁶ is independently selected from the group consisting of hydrogen, (C₁-C₆) alkyl, (C₅-C₁₀) aryl, five to sixteen membered heteroaryl, (C₆-C₁₆) arylalkyl and six to sixteen membered heteroarylalkyl; and

each K is independently selected from the group consisting of oxygen, nitrogen and sulfur.

14. The antimicrobial sulfonamide of Claim 13 in which each S¹ is independently a side-chain of a genetically encoded α -amino acid.

30 15. The antimicrobial sulfonamide of Claim 13 in which L is:



5 16. The antimicrobial sulfonamide derivative of Claim 15 in which each S¹ is independently a side-chain of a genetically encoded α -amino acid.

17. The antimicrobial sulfonamide derivative of Claim 15 in which n is 0.

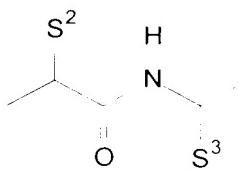
10 18. The compound of Claim 17 in which S¹ is hydrogen, Y² is decan-yl and R is the core cyclic peptide of aspartocin.

15 19. The antimicrobial sulfonamide derivative of Claim 17 in which S¹ is -CH₂-CO₂H, -CH₂-CH₂-CO₂H, -C(OH)H-CONH₂, -CH₂-CONH₂ or -CH₂-CH₂-CONH₂ or a salt or hydrate thereof.

20 20. The antimicrobial sulfonamide derivative of Claim 17 in which S¹ is -CH₂-indol-2-yl or -CH₂-phenyl.

21. The compound of Claim 20 in which R is the core antibiotic of laspartomycin and Y² is hexadecyl.

22. The antimicrobial sulfonamide derivative of Claim 13 in which L is:



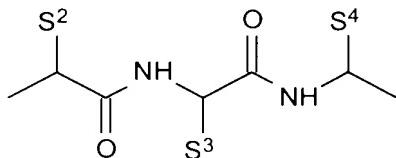
25 23. The antimicrobial sulfonamide derivative of Claim 22 in which S² and S³ are

each independently a side chain of a genetically encoded α -amino acid.

24. The antimicrobial sulfonamide derivative of Claim 22 in which S^2 is hydrogen, - CH_2 -indol-2-yl, - CH_2 -CONH₂ or - CH_2 -CH₂-CONH₂ and S^3 is - CH_2 -CO₂H,
5 - CH_2 -CH₂-CO₂H or a salt or hydrate thereof.

25. The antimicrobial sulfonamide derivative of Claim 22 in which S^2 is - CH_2 -CO₂H, - CH_2 -CH₂-CO₂H or a salt or hydrate thereof and S^3 is -C(OH)H-CONH₂.

10 26. The antimicrobial sulfonamide derivative of Claim 13 in which L is:



27. The antimicrobial sulfonamide derivative of Claim 26 in which S^2 , S^3 and S^4 are each independently a side chain of a genetically encoded α -amino acid.
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28. The antimicrobial sulfonamide derivative of Claim 26 in which S^2 is - CH_2 -indol-2-yl, S^3 is - CH_2 -CONH₂ or - CH_2 -CH₂-CONH₂ and S^4 is - CH_2 -CO₂H,
- CH_2 -CH₂-CO₂H or a salt or hydrate thereof.
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29. The antimicrobial sulfonamide derivative of Claim 26 in which S^2 is - CH_2 -indol-2-yl, S^3 is - CH_2 -CO₂H, - CH_2 -CH₂-CO₂H or a salt or hydrate thereof and S^4 is - CH_2 -CONH₂, - CH_2 -CH₂-CONH₂ or -C(OH)H-CONH₂.

25 30. The antimicrobial sulfonamide derivative of Claim 4 in which m is 0.

31. The antimicrobial sulfonamide derivative of Claim 30 in which R⁴ is hydrogen.
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32. The antimicrobial sulfonamide derivative of Claim 30 in which R is the core

antibiotic of laspartomycin or aspartocin.

33. The antimicrobial sulfonamide derivative of Claim 32 in which R is the core cyclic peptide of laspartomycin or aspartocin.

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34. A pharmaceutical composition comprising a compound according to Claim 4 and a pharmaceutically acceptable adjuvant, excipient, carrier or diluent.

10 35. A method for treating or preventing a microbial infection, said method comprising the step of administering to a subject a therapeutically effective amount of a compound according to Claim 4 or a therapeutically effective amount of a pharmaceutical composition according to Claim 34.

15 36. A method of inhibiting microbial growth, said method comprising the step of administering to a microbe an antimicrobially effective amount of a compound according to Claim 4 or an antimicrobially effective amount of a pharmaceutical composition according to Claim 34.

20 37. A method for making an antimicrobial sulfonamide derivative comprising sulfonylating an core antibiotic or core cyclic peptide with a lipophilic sulfonyl derivative, thereby providing a antimicrobial sulfonamide derivative.

25 38. The method of Claim 37 in which the lipophilic sulfonyl derivative is a activated lipophilic sulfonyl ester or a lipophilic sulfonyl halide.

39. The method of Claim 38 in which the activated lipophilic sulfonyl ester is a lipophilic hydroxybenzotriazole ester.

30 40. The method of Claim 39 in which the lipophilic sulfonyl halide is a lipophilic sulfonyl chloride.

41. A method for making an antimicrobial sulfonamide derivative comprising:

sulfonylating a linker with a lipophilic sulfonyl compound, thereby providing a lipophilic sulfonamide linker; and

covalently attaching the lipophilic sulfonamide linker to an core antibiotic or core cyclic peptide, thereby yielding a antimicrobial sulfonamide derivative.

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42. A method for making an antimicrobial sulfonamide derivative comprising:

covalently attaching a linker to an core antibiotic or core cyclic peptide, thereby providing an linker core antibiotic or linker core cyclic peptide; and

sulfonylating the linker core antibiotic or linker core cyclic peptide with a lipophilic sulfonyl derivative, thereby yielding a antimicrobial sulfonamide derivative.

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